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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,817	09/13/2005	Akira Matsuda	3691-011SPUS1	1607
2292 7590 06/07/2007 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER SHIN, DANA H	
			ART UNIT 1635	PAPER NUMBER
			NOTIFICATION DATE 06/07/2007	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No. 10/524,817	Applicant(s) MATSUDA ET AL.	
	Examiner Dana Shin	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 February 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>2-18-05</u> | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §1.821 through §1.825 for the reason(s) set forth below.

CFR §1.821(d) reads as follows:

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

Figure 7 of the instant application contains nucleic acid sequences which are not accompanied by "SEQ ID NO:". It is noted that applicant has filed amendments to the specification on September 13, 2005 to comply with sequence rules and submitted that the nucleic acid sequences in Figure 7 correspond to SEQ ID NOs:1-3. However, Figure 7 contains more than three distinct nucleic acid sequences, and therefore, it is unclear which SEQ ID NO represents which nucleic acids shown in Figure 7. Applicant is required to correct this deficiency. See Notice to Comply. Any response to this action must correct this deficiency, as this requirement will not be held in abeyance.

Status of Claims

Claims 1-6 are pending and currently under examination on the merits.

Information Disclosure Statement

The information disclosure statement filed on February 18, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Since the references listed in the IDS are applied against the claims in the instant case, the information referred to therein has been considered.

Nevertheless, applicant is required to submit a legible copy of citation Nos. BA and CA in response to this Office action in order to be compliant with 37 CFR 1.98(a)(2). The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper."

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Therefore, the references cited in the Search Report have not been considered unless cited herein.

Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Specification

The disclosure is objected for containing subject matter non-compliant with the requirements of 37 CFR §1.821 through §1.825. See above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

(c) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al. (*Chinese Science Bulletin*, 1993, 38:1177-1180, applicant's citation No. CB).

The claim is drawn to a 4'-thio-2'-deoxythymidine-5'-triphosphate compound.

Huang et al. teach a 4'-thio-2'-deoxythymidine-5'-triphosphate compound and that this compound can be used for antitumor and antiviral agents and for terminating DNA sequencing. See entire reference.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (US 6,004,939).

The claim is described above.

Chen et al. teach a 4'-thio-thymidine triphosphate compound (column 24, line 19).

Claim 2 is rejected under 35 U.S.C. 102 (a) as being anticipated by Minakawa et al. (*Journal of the Chemical Society Perkin Transactions 1*, 2002, 2182-2189).

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Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Minakawa et al. teach a compound comprising 4'-thio-cytosine and 5'-triphosphates (page 2182-2185).

Claims 1 and 5 are rejected under 35 U.S.C. 102(e) as being anticipated by Brown et al. (US 2003/0166282 A1).

The claims are drawn to an RNA comprising a 4'-thio-uridine-triphosphate and a method of synthesizing an oligonucleotide containing an RNA comprising a 4'-thio-uridine-triphosphate by conducting RNA chain elongation.

Brown et al. teach an siRNA oligonucleotide comprising 4'-thio-uridine-triphosphates (paragraphs 0050). They teach synthesizing siRNA oligonucleotides by conducting RNA chain elongation reaction via RNA polymerase, for example by PCR (paragraphs 0113, 0117-0119). Accordingly, all the claim limitations are taught by Brown et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 2003/0166282 A1) as applied to claims 1 and 5 above, further in view of Burgess et al. (*Chemical Reviews*, 2000, 100:2047-2059).

The claims are drawn to RNA and DNA containing a 4'-thioribonucleoside and 4'-thio-2'-deoxyribonucleoside, respectively, and methods of synthesizing them and producing oligonucleotides containing at least one 4'-thioribonucleoside and at least one 4'-thio-2'-deoxyribonucleoside.

Brown et al. teach that 4'-thio-uridine-triphosphates are incorporated into the siRNA oligonucleotide through enzymatic (PCR) or chemical synthesis (paragraphs 0051, 0117-0119). They teach that RNA oligonucleotides can be used as probes or gene expression studies (paragraph 0113). They teach that variations in the steps or sequence of steps of making the modified siRNAs comprising 4'-thio-uridine-triphosphates may be applied without undue experimentation (paragraph 0198). They teach that the siRNAs can contain DNA sequences (thymidine) instead of ribonucleotides (uracil). See paragraph 0109. Brown et al. do not teach a

DNA molecule comprising a 4'-thio-deoxynucleosides, nor do they teach a method for synthesizing 4'-thio-deoxynucleosides comprising reacting with pyrophosphoric acid.

Burgess et al. teach 28 different methods for nucleoside triphosphate synthesis. In particular, they teach that nucleoside triphosphates are synthesized by reacting with POCl_3 phosphorylation procedure, which yields nucleoside monophosphates, They teach that monophosphates are reacted with pyrophosphates to produce triphosphates. See entire reference. They teach that no method for preparing nucleoside triphosphates is suitable for all nucleobase derivatives; however, therapeutic applications of nucleoside inhibitors in the art have prompted chemists to explore various venues for efficient triphosphate synthesis procedures (page 2058).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize 4'-thio-2'-deoxynucleoside-triphosphates by modifying various methods of synthesizing nucleoside triphosphates of Burgess et al., in order to incorporate the synthesized 4'-thio-2'-deoxynucleoside-triphosphates into the siRNA molecule of Brown et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because the benefit of incorporating 2'-thionucleotides into oligonucleotides (e.g., siRNA) was known in the art as taught by Brown et al., and because various methods of synthesizing nucleoside triphosphates for different nucleobase derivatives were known in the art as taught by Burgess et al. Since the need for different methods for different nucleobase derivatives was recognized as taught by Burgess et al. (page 2058), and since siRNAs comprising 4'-thionucleotides were known to confer enhanced gene inhibition as taught by Brown et al. (paragraphs 0050-0051, 0109, 0113, 0117-0119), and since Brown et al. taught that siRNAs can comprise DNAs (paragraph 0109) and that variations in the steps of

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making the modified siRNAs comprising 4'-thio-uridine-triphosphates may be modified and applied without undue experimentation (paragraph 0198), the skilled artisan would have been motivated to devise a method of synthesizing 4'-thio-deoxynucleoside triphosphates through routine optimization screening and trial/error experimentation, and thereby arriving at the instantly claimed invention with a reasonable expectation of success. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635


J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 37 CFR §1.821(g). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. §§1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. §§1.821-1.825. Applicants attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. §1.821(c).
- ☐ 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. §1.821(e).
- ☐ 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. §1.822 and/or 1.823, as indicated on the attached copy of the marked-up Raw Sequence Listing.
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. §1.825(d).
- ☐ 6. The paper copy of the Sequence Listing is not the same as the computer readable form of the Sequence Listing as required by 37 C.F.R. §1.821(e).
- ☐ 7. Other:

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the Sequence Listing. (If the unidentified sequences are not provided on the CRF)
- ☒ An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification. (If the unidentified sequences are not provided in the paper copy)
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). (If a new paper and/or CRF are required)

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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